Remarks

Claims 1-15 and 29-52 are pending in the application. Claims 1-15, 29, 40, 41, 45 and 46 have been withdrawn from consideration pursuant to a restriction requirement. Claims 34 and 35 have been withdrawn as being directed to nonelected species of invention. Claims 30-33, 36-39, 42-44 and 47-52 stand rejected. Reconsideration is requested in view of the above changes and the following remarks.

Sequence Listing

A substitute sequence listing is submitted herewith, to add the nucleotide sequence at page 51, line 21 as SEQ ID NO:3. No new matter is introduced. A Statement Under 37 C.F.R. 1.825 appears at the foot of this document.

The specification has been amended at page 51 to refer to the aforesaid sequence as "SEQ ID NO:3". The specification was further amended at lines 18-20 to refer to the sequences set forth therein as "SEQ ID NO:1" and "SEQ ID NO:2", respectively. No new matter is introduced.

Request for Rejoinder of Claims

The elected group, i.e., new Group IV, contains claims 30-39, 42-44 and 47-52. However, claims 34 and 35 have been withdrawn from consideration as being allegedly drawn to a non-elected species.

It is respectfully submitted that Examiner has made an error in withdrawal of claims 34 and 35 for two reasons. First, claim 34 recites, as one alternative, the drug CPT-11, which is a topoisomerase inhibitor. Thus, claim 34 is consistent with the election of topoisomerase inhibitor as the chemotherapeutic agent. Second, the examiner has withdrawn the species requirement for "chemotherapeutic agent". Thus, all claims in the elected group must be examined, without regard to the recitation of specific chemotherapeutic agent. For the same reason, claim 35 should not be withdrawn from consideration. Third, it appears that 34 has been rejoined *sub silento* anyway, notwithstanding the indication to the contrary at page 3 of the Detailed Action. Claim 34 was included in the rejections that have been asserted.

Clarification of the record and rejoinder of claims 34 and 35 with the examined claims is respectfully requested.

Response to 35 USC 103 Rejections

Claims 30, 31, 34, 36-39, 42, 47 and 49-52 have been rejected under 35 USC 103 as being allegedly unpatentable over Siegmund *et al.* in view of Xiang *et al.*

The Examiner argues that, as Siegmund *et al.* teaches that tumour cell sensitivity to TRAIL-induced apoptosis can be enhanced by treatment with siRNA directed to c-FLIP, and Xiang *et al.* discloses that tumour cell sensitivity to TRAIL-induced apoptosis can be enhanced by treatment with CPT-11, one of ordinary skill in the art would have been motivated to combine the teaching of the two documents to obtain the benefit of each component (i.e. c-Flip siRNA and CPT-11 in enhancing TRAIL-induced apoptosis of tumour cells).

Applicants respectfully disagree. The skilled person would, if anything, be taught by Siegmund not to combine chemotherapeutic drugs with TRAIL-based therapy, in particular in the presence of c-FLIP RNAi-based therapies, given that Siegmund explicitly teaches that chemotherapy can have a broad range of unwanted side effects and, importantly, that the solution to the side effect problem is the replacement of chemotherapy with therapies based on the inhibition of c-FLIP expression. Examiner's attention is respectfully directed to the abstract of Siegmund, in particular the penultimate three sentences of the Background section, which teach that c-FLIP targeted therapies are more specific for sensitizing tumour cells to TRAIL than chemotherapy. Attention is also directed to the Siegmund abstract's Conclusion which teaches that inhibition of c-FLIP expression "was sufficient to sensitise tumour cells for TRAIL-induced apoptosis".

The suggestion by Siegmund that c-FLIP inhibition should be used *in place of and not in addition to* chemotherapy is further clarified by paragraph 2, column 1, page 76, which again repeats that siRNA against c-FLIP is sufficient to sensitize tumour cells to TRAIL-mediated apoptosis and that "the implementation of this selected RNA targeting approach in TRAIL-based therapies opens the possibility to *circumvent broad effects common to chemotherapeutic drugs*" (emphasis added). The message is further emphasized on page 731, first column, second

paragraph, which, in the first sentence, emphasizes that TRAIL may exert certain toxic effects on normal tissue when combined with chemotherapeutic drugs. Later in the same paragraph, Siegmund states that "Because RNA interference is much more selective than chemotherapeutic drugs siRNAs could efficiently sensitise for TRAIL-induced apoptosis with a considerably reduced risk of side-effects compared with chemotherapy."

Therefore, Siegmund teaches that combination therapies involving chemotherapy and TRAIL, such as that taught by Xiang, are associated with side effect problems which can be circumvented by the use of c-FLIP-based therapies in combination with TRAIL instead of chemotherapy with TRAIL.

Therefore, it is incorrect to state that one skilled in the art would be motivated to combine the use of c-FLIP and chemotherapy and TRAIL in a single treatment. Indeed, the opposite is true. One or ordinary skill in the art would have been led away from making the claimed invention from the asserted combination of references.

Examiner alleges that the idea of combining siRNA of Siegmund with the CPT-11 of Xiang logically flows from their having been individually taught in the prior art. The Examiner cites MPEP 2144.06(l) in this regard. But it is also true that the prior art must be considered in its entirety, including disclosures such as those discussed above that teach away from the claimed invention (MPEP 214.02). Likewise, the proposed modification, (here, the modification of Sigmund to add CPT-11 to the c-Flip siRNA of Siegmund) cannot render the prior art unsatisfactory for its intended purpose, or change the principle of operation of a reference (MPEP 2143.01). A prior art reference that "teaches away" from the claimed invention is a significant factor to be considered in determining obviousness. MPEP 2145(X)(D)(1); it is improper to combine references where the references teach away from their combination. MPEP 2145(X)(D)(2).

Thus, the invention of claims 30 and 42 is not *prima facie* obvious over Siegmund in view of Xiang. Moreover, the invention results in the unexpected synergism which further supports nonobviousness. Compositions such as those of claim 30, *i.e.* comprising a c-FLIP inhibitor and a chemotherapeutic agent, such as a thymidylate synthase inhibitor, oxaliplatin or a topoisomerase I inhibitor, are demonstrated to exert supra-additive effects in the killing of cancer

cells. Evidence of such synergy, as presented in the Specification of the present application, is plentiful. For example, the co-treatment of FT siRNA transfected HCT116p53$^{+/+}$ cells with the thymidylate synthase inhibitor 5-FU resulted in a supra-additive increase in apoptosis, where approximately 43% of the cells undergoing apoptosis as compared to approximately 11% in cells treated with 5-FU and the control siRNA. Further, the co-treatment of FT siRNA transfected cells with oxaliplatin resulted in approximately 61% of the cells undergoing apoptosis as compared to approximately 17% in cells treated with oxaliplatin and the control siRNA (See Specification at p.62, lines 17-28 and Figure 11B). A similar synergistic effect was evidenced by down-regulating of c-FLIP on apoptosis induced by the topoisomerase I inhibitor CPT-11 (See Specification at p.63, lines 25-32 and Figure 10C). Also, co-treatment of FT siRNA-transfected p53 null HCT116 cells with 5-FU, oxaliplatin or CPT-11 all showed highly significant increases in cells undergoing apoptosis (See Specification at p.67, lines 5-20 and Figures 12A-C) In yet another example, RKO cells co-treated with FT siRNA and CPT-11 resulted in approximately 43% of the cells undergoing apoptosis as compared to approximately 15% of the control co-treatment (See Specification at p.68, line 28 to p.69, line 10 and Figure 13C). In each such case, the effects of co-treatment of FT siRNA with the aforementioned chemotherapeutic agents was more than additive, and indicates a strong synergistic interaction as between a c-FLIP inhibitor such as FT siRNA and each chemotherapeutic agent.

The result is even more indicative of the nonobviousness of the invention of claims 49-52, which define combinations of c-FLIP inhibitor and the selected chemotherapeutic agents in the absence of a death receptor binding member such as TRAIL. Siegmund and Xiang relate to methods of enhancing sensitivity of tumour cells to TRAIL. Thus, even if it could be argued that the skilled artisan would consider combining the teachings of Siegmund and Xiang in order to enhance sensitivity of tumour cells to TRAIL, the demonstration by the present inventors that synergistic effects in the killing of tumour cells may be obtained *in the absence of TRAIL* is unexpected, specifically, that treatment with combinations of the specific chemotherapeutic agents recited in the claims such as topoisomerase I inhibitors and c-FLIP inhibitors in the absence of TRAIL, would not be expected to demonstrate any benefit, let alone a supra-additive effect..

For the foregoing reasons, claims 30 and 42, respectively defining compositions and kits comprising the combination of (a) a c-FLIP inhibitor and (b) a chemotherapeutic agent, which is thymidylate synthase inhibitor, oxaliplatin or a topoisomerase I inhibitor, are allowable over Siegmund *et al.* in view of Xiang *et al.*

Claims 31, 34, 36-39, 47 and 49-52 depend directly or indirectly form either claim 30 or 42. In view of the allowability of claims 30 and 42, claims 31, 34, 36-39, 47 and 49-52 are likewise allowable.

Claims 49-52 recite a further feature that distinguishes the over the prior art, namely that the claimed combination does not include a death receptor binding member such as TRAIL. As indicated above, each of Siegmund and Xiang relate to methods of enhancing sensitivity of tumour cells to TRAIL. Thus, even if it could be argued that the skilled artisan would consider combining the teachings of Siegmund and Xiang in order to enhance sensitivity of tumour cells to TRAIL, the presence of TRAIL is a requirement. The skilled artisan would not make a combination of a c-FLIP inhibitor and a chemotherapeutic agent without also including TRAIL. Thus, the asserted combination of references teaches away from compositions such as those of claim 49-52 that would not include TRAIL. The finding by the present inventors that an effect in killing of tumour cells may be obtained *in the absence of TRAIL* is unexpected. The finding is even more unexpected given that the effect of the combination of c-FLIP inhibitor and selected chemotherapeutic agent was supra-additive.

Claims 43, 44 and 48 have been rejected under 35 USC 103 as being allegedly unpatentable over Siegmund *et al.* in view of Xiang *et al.* as applied to claims 30, 31, 34, 36-39, 42, 47 and 49-52, further in view of Tuschl *et al.* US Pat. Pub 20040259247 ("Tuschl (1)") and Tuschl *et al.*, "The siRNA User Guide" ("Tuschl (2)".

Claims 43 and 44 are independent claims reciting an RNAi agent having or consisting of the nucleotide sequence SEQ ID NO:1 or SEQ ID NO:2. Claim 48 depends indirectly from claim 30, and recites the same sequences.

Although none of the above references teaches an siRNA comprising either SEQ ID NO: 1 or SEQ ID NO: 2, the Examiner considers that it would have been obvious to design these

specific siRNA. The prior art is regarded by Examiner as providing a wealth of information on the design of siRNAs.

Claim 48 is dependent on claim 30 and therefore includes all the features of claim 30. For the reasons set forth above, claims 30 is allowable over the combination of Siegmund and Xiang. The two Tuschl references do not remedy the deficiencies of the Siegmund/Xiang combination. Thus, claim 48 is allowable over the asserted combination of Sigmund, Xiang and the two Tuschl references.

Moreover, applicants respectfully disagree with the Examiner's assertions that the specific siRNA SEQ ID NO:1 or NO:2 molecules as claimed *per se* (claims 43 and 44) or as part of a composition comprising a thymidylate synthase inhibitor, oxaliplatin or a topoisomerase I inhibitor (claim 48), or indeed any siRNA molecules to c-FLIP (as alleged by the Examiner), would have been obvious in view of the cited prior art. As acknowledged by the Examiner, merely employing the algorithms and methods recited in the prior art for designing RNAi sequences to a target does not guarantee that the siRNA sequences designed will have any activity. Nevertheless, even if it could be argued that it is routine to produce functional siRNA molecules against cFLIP, cFLIP siRNA molecules having (i) the structures of specific sequences SEQ ID NO 1 or SEQ ID NO 2 as claimed and (ii) the activity associated with these specific molecules, could not be predicted. As demonstrated in the Examples of the present application, the siRNA molecules as claimed in claims 43 and 44 are extremely potent compared to other siRNA molecules, the SEQ ID NO 1 and SEQ ID NO 2 siRNA molecules working exquisitely at sub-nanomolar concentrations. Structurally, with respect to the SEQ ID NO 1 and SEQ ID NO 2 molecules, the Examiner has not cited any document that would direct the skilled artisan to produce these specific molecules. Moreover, the skilled person would have no reason to expect any c-FLIP inhibitory activity for such molecules, let alone the potent activity demonstrated by the present application. Thus, the skilled person wishing to produce RNAi agents with activity against c-FLIP, would not have been motivated to modify known RNAi agents of known activity in order to produce the specifically claimed SEQ ID NO 1 and SEQ ID NO 2 molecules with any expectation of success that such molecules would have the potent activity as demonstrated in the present specification.

For the foregoing reasons, claims 43, 44 and 48 are allowable over Siegmund in view of Xiang, and the Tuschl references.

Claims 30-34, 36-39, 42, 47 and 49-52 have been rejected under 35 USC 103 a being allegedly unpatentable over Hyer *et al.*, Uslu *et al.*, Ni *et al.* and Tuschl *et al.* U.S. Pat. 7,056,704.

The Examiner alleges that Hyer *et al.* teaches a method of killing DU145 prostate cancer cells comprising administration of a c-FLIP antisense oligonucleotide and CH11 antibody (FAS antibody; see claim 33). Uslu *et al.* teaches the treatment of prostate cancer cell lines with chemotherapeutic agents (in particular CDDP, adriamycin and etoposide) and CH11 antibodies. Ni *et al.* teaches a number of specific chemotherapeutic agents.

The Examiner alleges that it would have been *prima facie* obvious to prepare a composition comprising the c-FLIP antisense and CH11 antibody as taught by Hyer and the chemotherapeutic agent as taught by Uslu or Ni. Applicants respectfully disagree, for the following reasons.

First, given the teaching of Siegmund that c-FLIP inhibition may be used to substitute for chemotherapeutic agents and circumvent undesirable side-effects of such agents, the skilled artisan would not have considered providing compositions and methods involving both c-FLIP inhibitors and chemotherapeutic agents.

Second, Examiner's remarks are based on an overgeneralization of the significance of the teaching of the asserted prior art documents. Uslu *et al.*, for example, teaches that certain prostate cancer cell lines may be sensitized to CH-11 antibody treatment using certain chemotherapeutic agents. The document merely teaches that specific chemotherapeutic agents (CDDP, adriamycin and VP-16) sensitize specific prostate cancer cell lines to anti-FAS antibody therapy. The document clearly teaches on page 968, column 2, section 1 that the effect shown for adriamycin and VP-16 (and CDDP) was not demonstrated for another chemotherapeutic agent, suramin, thus demonstrating that the effect of sensitizing the specific prostate cancer cell lines tested with CH-11 was specific to the particular chemotherapeutic agents tested.

Moreover, the same section of Uslu *et al.* teaches that the demonstrated effects were specific to particular prostate cancer cell lines, with the LnCAP line *not* demonstrating

sensitization to anti-FAS antibodies with the three specific chemotherapeutic agents which worked on the DU145 and PC-3 cell lines. Thus, Uslu teaches that the effect demonstrated therein is *both* chemotherapeutic agent-dependent *and* prostate cancer cell line-dependent.

Thus, the skilled person would not consider substituting one of the chemotherapeutic agents recited in Ni for one of the chemotherapeutic agents recited in Uslu, given that Uslu teaches that only certain specific chemotherapeutic agents have the desired effect with respect to sensitization to CH-11.

The independent claims subject to rejection, claims 30 and 42, recite combinations of (a) a c-FLIP inhibitor and (b) a thymidylate synthase inhibitor, oxaliplatin or a topoisomerase I inhibitor. None of the chemotherapeutic agents recited by Uslu fall within these categories. One of ordinary skill in the art would not expect that substitution of the chemotherapeutic agents used by Uslu with one of the chemotherapeutic agents recited in the claims, e.g., a topoisomerase I inhibitor, would result in the synergistic effect as demonstrated by the present invention in the killing of cancer cells.

For the avoidance of any doubt on the part of the Examiner, both adriamycin and VP-16, as employed by Uslu, are topoisomerase II inhibitors and not topoisomerase I inhibitors. As the Examiner will be aware, topoisomerase II inhibitors and topoisomerase I inhibitors differ in their use clinically and are used on different cancers. This, of course, is consistent with the teaching of Uslu that the effects demonstrated therein were chemotherapeutic agent-dependant and indeed prostate cancer cell line-dependent.

Moreover, as Hyer *et al.* is directed to the use of c-FLIP antisense to sensitize cancer cell lines to treatment with CH-11, even if the skilled person were to consider adding a chemotherapeutic agent, given the teaching of Uslu that only specific chemotherapeutic agents have an effect of the sensitization of prostate cancer cells to CH-11, the skilled person would have selected one of the chemotherapeutic agents taught by Uslu as being efficacious in this regard, and not one of the agents recited in the present claims, *i.e.*, thymidylate synthase inhibitor, oxaliplatin or topoisomerase I inhibitor.

Such an outcome can only be reached by ignoring the teaching of the prior art, especially Siegmund and Uslu, and by applying hindsight reasoning and the knowledge of the teaching of the present invention.

For the foregoing reasons, claims 30 and 42 are allowable over the asserted reference combination.

Claims 31-34, 36-39, 47 and 49-52 depend directly or indirectly form either claim 30 or 42. In view of the allowability of claims 30 and 42, claims 31-34, 36-39, 47 and 49-52 are likewise allowable.

Conclusion

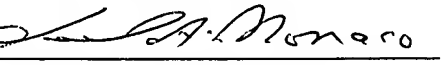
The claims remaining in the application are believed to be in condition for allowance. An early action toward that end is earnestly solicited.

Statement Under 37 C.F.R. §1.825

The sequence listing information recorded on the substitute computer readable form is identical to the written (on paper) substitute sequence listing submitted herewith. The substitute Sequence Listing includes no new matter.

Respectfully submitted,

PATRICK GERARD JOHNSTON, *et al.*

BY 

DANIEL A. MONACO
Registration No. 30,480
DRINKER BIDDLE & REATH LLP
One Logan Square
18th and Cherry Streets
Philadelphia, PA 19103-6996
TEL: (215) 988-3312
FAX: (215) 988-2757
Attorney for Applicants